Conclusion: The combination of nonspecific clinical signs (pain, dyspepsia) with biochemical markers of biliary pathology and endocrine pancreatic insufficiency – of PCa patients demonstrates the obligatoriness of differential diagnostic pancreatic and biliary pathology in their earlier stages.

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P119Cell aggregation increases drug resistance of acute myelomonocytic leukemia cells

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Acute myelomonocytic leukemia (FAB M4) is one of the most common forms of acute myeloid leukemia (AML). This AML form is characterized by rapid accumulation transformed myeloblasts and monoblasts in bone marrow, with the rapid suppression of normal hematopoiesis. Bone marrow microenvironment is one of the main factors determining drug resistance of leukemic cells. It is known that the adhesion of leukemic cells to mesenchymal stem cell and bone marrow extracellular matrix (laminin, collagen) enhances their drug resistance. However, it remains unknown whether the emergence of drug resistance when cell–cell contacts are formed only between leukemia cells, without the involvement of bone marrow stromal elements. We studied the role of cell aggregation in drug resistance of leukemic cells. We used the bone marrow mononuclear cells (BMMC) isolated from the patients with acute myelomonocytic leukemia. For the formation of multicellular aggregates, BMMC were cultivated in 96-well plates coated with 1.5% agarose. We showed that resistance of BMMC to bortezomib, doxorubicin and fludarabine in multicellular aggregates was increased. In three-dimensional multicellular aggregates of BMMC index IC50 for bortezomib, doxorubicin and fludarabine was 7 ± 1 ng/ml, 1 ± 0.4 mkM and 0.8 ± 0.05 mkM, respectively. In control condition, index IC50 bortezomib, doxorubicin and fludarabine was significantly lower, 2 ± 0.5 ng/ml, 0.3 ± 0.05 mkM and 0.07 ± 0.001 mkM, respectively. In multicellular aggregates of BMMC number of mitotic cells and expression of Ki-67 protein were not significantly different from the control. It has also been shown that cells in multicellular aggregates increased expression antiapoptotic protein Bcl-2. Suppression of BMMC aggregation by culturing the cells in medium containing 0.9% methylcellulose resulted in decreased IC50 index for bortezomib, doxorubicin and fludarabine, 2 ± 0.7 ng/ml, 0.12 ± 0.004 mkM and 0.04 ± 0.005 mkM, respectively. Expression of the Bcl-2 protein was also decreased. This work demonstrates the involvement of cell aggregation in the formation of drug resistance phenotype in leukemic cells.

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Blood-based biomarkers for lung cancer

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Blood-derived biomarkers, such as circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA), are a valuable source of molecular genetic data for tumours they spring from. In translational cancer research, the "liquid biopsy" concept has been put forward to denote the detection and molecular characterization of these biomarkers.

The idea of liquid biopsy is based on a hypothesis that profiles of somatic mutations in CTCs and ctDNA are identical to those in the original tumour. Therefore, the mutation status of the source tumour can be revealed through the molecular analysis of the CTCs and ctDNA obtained from the blood. The major advantages of liquid biopsy are an essentially decreased invasiveness (no need for tissue biopsy, surgery or bronchoscopy) and an ability to carry out the analysis at patient's follow up (e.g. to monitor for residual disease).

However, both the CTCs and ctDNA are not abundant in the bloodstream and their capture is technically challenging. Also, due to tumour heterogeneity, the CTCs may not fully represent the entire tumour, while ctDNA is naturally fragmented and degraded, so its utility for genetic analysis may be limited. Finally, the DNA extracted from CTCs and, especially, ctDNA are "contaminated" by DNA from non-tumour cells from the bloodstream raising a challenge of detecting mutant DNA among significantly prevailing wild-type DNA.

Some of these issues can be overcome by using such advanced techniques as BEAMing, digital PCR or ultra-deep sequencing, but their use in standard clinical settings is limited by the need for special equipment and associated costs. Inexpensive and less sophisticated, but still highly sensitive and specific, approaches, such as COLD-PCR or wild-type blocking PCR, are also available to detect "druggable" mutations in CTCs and ctDNA.

Application of these approaches of liquid biopsy in clinical practice may be highly beneficial for personalized care of lung cancer patients.

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Endogenous inhibitors of cysteine proteases and preform of cathepsin B in cancer of reproductive system